Dorsal-Ventral Patterning of the Developing Forebrain: Towards an Understanding Holoprosencephaly

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Proper dorsal-ventral patterning in the developing central nervous system (CNS) requires signals from both the dorsal and ventral neural tube. Data from multiple studies have demonstrated that bone morphogenetic proteins (BMP) and sonic hedgehog (Shh) protein are secreted factors that regulate dorsal and ventral specification respectively within the caudal neural tube. In the developing rostral CNS Shh also participates in ventral regionalization, however, the roles of BMP's in the developing brain are less clear. We hypothesized that BMP's also play a role in dorsal specification of the vertebrate forebrain. To test our hypothesis we implanted beads soaked in recombinant bone morphogenetic protein 5 or 4 into the neural tube of the chick forebrain. Experimental embryos showed a loss of the basal telencephalon that resulted in holoprosencephaly (a single cerebral hemisphere), cyclopia (a single midline eye) and loss of ventral midline structures. In situ hybridization using a panel of probes to genes expressed in the dorsal and ventral forebrain revealed the loss of ventral markers with the maintenance of dorsal markers. Furthermore, we found that the loss of the basal telencephalon was the result of excessive cell death and not a change in cell fates. These data provide evidence that BMP signaling participates in dorsal-ventral patterning of the developing brain in vivo, and disturbances in dorsal-ventral signaling result in specific malformations of the forebrain.

To further characterize the mechanisms of dorsal-ventral patterning in the developing forebrain we have begun examining the expression of multiple genes along the dorsal-ventral axis of the developing neural tube. Development of the rostral neural tube of vertebrates involves the transition from a single prosencephalic vesicle to bilaterally symmetric telencephalic vesicles and a single diencephalic vesicle. The diencephalic derivatives in the mature brain include the epithalamus, thalamus, and hypothalamus. The mature diencephalon is functionally and anatomically parceled into well-defined nuclei, features that resemble more caudal regions of the central nervous system (CNS). The existence of discrete and identifiable nuclei located along the anterior-posterior (A/P) and dorsal-ventral (D/V) axes makes the diencephalon an attractive model system to study the mechanisms of pattern formation within the developing forebrain. In the spinal cord, D/V identity is set up by extrinsic signals and propagated through the action of a series of homeodomain transcription factors. Consequently, distinct expression domains of these transcription factors specify D/V identity of neural progenitor cells in the ventricular zone. To begin investigating whether more rostral parts of the CNS use a similar mechanism of D/V patterning to that of the spinal cord, we have focused on the expression domains of a series of the transcription factors in the developing diencephalon: cLhx2b, cZic1, cZic3, and Pax6. Our data show that these transcription factors are predominantly expressed in distinct domains of the dorsal diencephalon with partial overlap and that there is a correlation between their expression domains in the proliferating zone and in differentiated nuclei of the developing diencephalon. These results are consistent with the hypothesis that regionalization of the diencephalon occurs in progenitor cells of the ventricular zone and that this regional identity is maintained in differentiated nuclei. This supports our hypothesis that specific nuclei in the forebrain may be specified along the dorsal-ventral axis in an analogous fashion to spinal cord cell specification.

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